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Clinical study of biological response modifiers as maintenance therapy for hepatocellular carcinoma

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Abstract. We conducted a randomized, controlled trial comparing 5-fluorouracil (5-FU) with or without biological response modifiers (BRMs) as a maintenance therapy for hepatocellular carcinoma (HCC) after treatment with percutaneous ethanol injection (PEI), transcatheter arterial embolization (TAE) or arterial infusion of antitumor agents (AI). A total of 58 cases of HCC were classified into 4 groups as follows: group I, PSK with 5-FU (n = 15); group II, lentinan with 5-FU (n = 15); group III, OK-432 with 5-FU (n = 12); and group IV, 5-FU alone as the control (n = 16). The mean survival time, mortality rate, time to progression, and T_4/T_8 ratio of lymphocytes in the peripheral blood were compared among the four groups. There was no significant difference in the background factors among the groups. In group I, the T_4/T_8 ratio of lymphocytes was reduced after the therapy. No significant difference was found among the groups in terms of the mean survival time, mortality rate, or time to progression. PEI for initial therapy was superior to the other therapies in terms of the mean survival time and mortality rate. These results suggest that the addition of BRM to maintenance therapy with 5-FU exerts no prognostic benefit on HCC patients treated with PEI, TAE, or AI.

Introduction

Percutaneous ethanol injection (PEI), transcatheter arterial embolization (TAE), and arterial infusion of antitumor agents (AI) are being established as effective therapies for patients with inoperative hepatocellular carcinoma (HCC) [1, 4, 9]. However, these methods are not suitable for maintenance therapy after tumor reduction or a relative decrease in size because, depending on the patient's condition, they cannot be performed on a long-term basis.

There have been quite a few reports concerning the treatment of HCC with biological response modifiers (BRMs), and the effectiveness of BRMs for HCC patients has not been established. We conducted a randomized controlled trial comparing 5-fluorouracil (5-FU, tablet) with or without BRMs as maintenance therapy for HCC after treatment with PEI, TAE, or AI.

Materials and methods

1. Research period and institution. From June 1987 to October 1992, a joint study was conducted in our department and the branch institutions shown in Table 1.

2. Patients. Patients with HCC who had been treated with PEI, TAE, or AI and showed a therapeutic effect of at least "no change" (NC) as evaluated by the criteria of the Japan Society for Cancer Therapy were eligible for this study. The entry requirements included an expected survival of more than 3 months, the absence of any serious cardiac or renal problem, the absence of hypersensitivity to OK-432, a minimal white blood cell count of 2,000/mcl, a minimal platelet count of 4×10^4/mcl, and a minimal hemoglobin concentration of 8 g/dl. In all cases, informed consent was obtained from the patient or a family member.

3. Treatment. The method of administration of BRMs was as follows. All patients were given 5-FU orally at 100–150 mg every day. They

Table 1. Cooperating institutions

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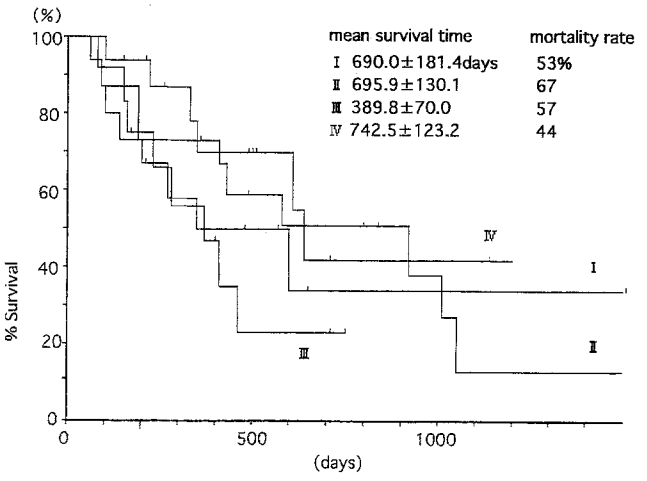

Fig. 1. Survival by treatment group

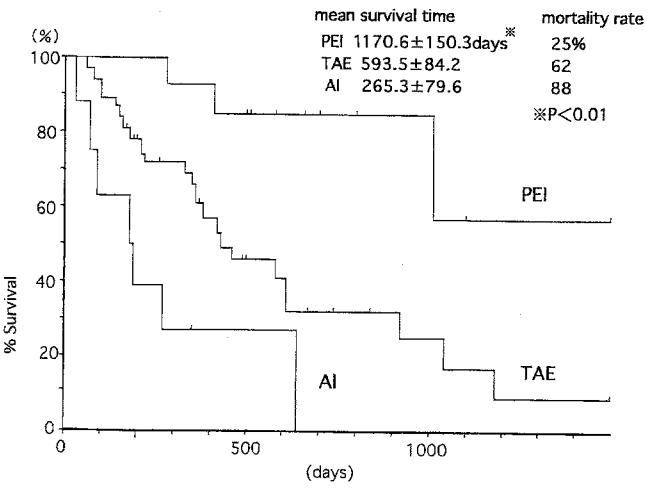

Fig. 2. Survival as a function of the initial therapy

Table 2. Patients' characteristics

Characteristic	Group				Total
	I	II	III	IV	
No. of patients	15	15	12	16	58
Sex:					
M	11	12	8	9	40
F	4	3	4	7	18
Age (mean, years)	58	62	65	66	62
Child's classification:					
A	7	8	4	11	30
B	3	7	6	5	21
C	5	0	2	0	7
Initial therapy:					
PEI	7	10	8	13	38
TAE	3	3	4	2	12
AI	5	2	0	1	8

were allocated into four groups. Group I was given 3 g PSK orally every day for 7 consecutive days every 2 weeks. Group II was intravenously injected with 2 mg of lentinan (LTN) once every week. In group III, OK-432 was subcutaneously injected once per week, and the dose was gradually increased from 0.2 KE to 5 KE, depending on the patient's condition. Group IV was given a daily dose of only 100–150 mg 5-FU orally (active control). Allocation was done randomly by the envelope method. Observation of the general condition, laboratory tests, tumor marker tests, and various image diagnoses were performed once a month, in principle. The mean survival time, mortality rate, time to progression, and T_4/T_8 ratio of lymphocytes in the peripheral blood were also determined.

Results

1. Enrolled cases

A total of 65 patients were entered into this study, including 16 in group I, 16 in group II, 17 in group III, and 16 in group IV. In all, 3 ineligible patients were completely excluded from the analyses. The remaining 62 patients consisted of 58 protocol-adhering patients and 4 patients who violated the protocol because of side effects due to BRMs. Finally, 58 of the 65 patients enrolled (89%) were included in the analyses, including 15 in group I, 15 in group II, 12 in group III, and 16 in group IV.

Table 3. Time to progression in each treatment group

Group	Time to progression (days)	Significance level
I	250,2 ± 153.7	NS
II	344.1 ± 266.3	NS
III	252.2 ± 199.3	NS
IV	299.3 ± 209.5	NS

NS, Not significant

Table 4. Change in the T_4/T_8 ratio after BRM

Group	Before BRM	After BRM
I	2.33 ± 1.63	1.91 ± 1.25*
II	2.23 ± 1.36	2.20 ± 1.21
III	2.12 ± 1.13	2.40 ± 1.39
IV	1.99 ± 0.50	2.07 ± 0.69

* $P < 0.05$

2. Analyzed cases

Table 2 presents the background characteristics of the patients; there was no significant difference in sex, average age, Child's classification, or previous treatments. However, five of the seven Child's C cases were in group I and two were in group III, whereas five of the eight AI cases were in group I. Thus, group I showed a tendency to include more cases with rather deteriorated reserve liver function.

The survival rate of each group was determined by the Kaplan-Meier method (Fig. 1). The mean survival time was 690.0 ± 181.4 days in group I, 695.9 ± 130.1 days in group II, 389.8 ± 70.0 days in group III, and 742.5 ± 123.2 days in group IV, with no significant difference being found among them. The mortality rate was 53% in group I, 67% in group II, 57% in group III, and 44%

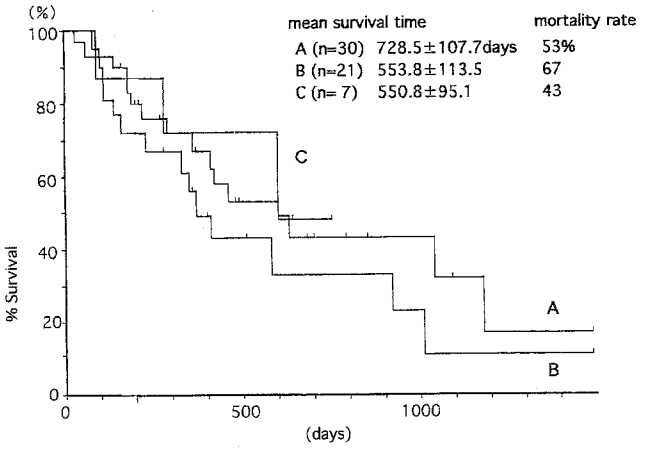

Fig. 3. Survival as a function of the Child's classification

Table 5. Mean survival time and mortality rate as a function of tumor size

Size (cm)	Mean survival time (days)	Mortality rate (%)
≦2 (n = 18)	759.8 ± 109.8	46
2~5 (n = 29)	687.3 ± 112.1	52
>5 (n = 16)	509.5 ± 106.4	75

in group IV. The mean time to progression was 250.2 ± 153.7 days in group I, 344.1 ± 266.3 days in group II, 252.2 ± 199.3 days in group III, and 299.3 ± 209.5 days in group IV, and the differences among the groups were not significant (Table 3). The T_4/T_8 ratio of lymphocytes in the peripheral blood did not change after the BRM therapy for more than 3 months except in group I, where the ratio decreased after the therapy (Table 4).

A study was made of the factors affecting the patients' survival. The mean survival time compared as a function of the previous therapy was 1170.6 ± 150.3 days for PEI, 593.5 ± 84.2 days for TAE, and 265.3 ± 79.6 days for AI, and the survival rate was significantly higher for PEI than for the other two groups (Fig. 2). The mortality rate was 25% for PEI, 62% for TAE, and 88% for AI, showing the same favorable tendency for PEI. The mean survival time compared as a function of the Child's classification was 728.5 ± 107.7 days for Child's A, 553.8 ± 113.5 days for Child's B, and 550.8 ± 95.1 days for Child's C, with no clear difference being found among the Child's classification groups (Fig. 3). The tumors were divided into three groups on the basis of the diameter being 2 cm or less, 5 cm or less, and more than 5 cm, and the average survival and mortality were compared. No clear difference in mean survival time was observed among the three groups (Table 5).

Discussion

Recently, the mortality due to HCC has been increasing in Japan, and various therapies are being tried against it. At present, PEI and TAE are considered to be effective and are frequently used for inoperable HCC. However, these methods are not suitble for long-term maintenance therapy and should be used once or a limited number of times for remission induction. For maintenance, the use of oral drugs other than 5-FU or UFT is rare, and few studies have been conducted on other therapeutic methods [3, 5].

BRMs are considered to act as enhancers of the antitumor effects of radiation and chemotherapies, thereby preventing the recurrence or metastasis of cancer after surgery [7]. It has been postulated that in patients with HCC, the immunity is generally lowered due to the cancer itself and to cirrhosis, which is often a complication of HCC in Japan [6].

Under these circumstances, we concluded that it was necessary to carry out a randomized control study of the various effects of BRMs as maintenance therapy after the performance of PEI, TAE, or AI. We thus started a cooperative study at several research institutions.

Three kinds of BRM, i.e., PSK, LTN, and OK-432, which are generally used for other solid cancers, were selected and compared with one another. In the present study, the BRM therapy was not effective since the results did not show any clear difference from those obtained in the control group. Hirai et al. [2] reported that concurrent use of carmofur or tegafur with OK-432 for maintenance therapy after TAE was effective. However, some difference was demonstrated in our study, in which the previous therapy was different from that used by Hirai et al. Furthermore, although no significant difference was found, there may have been some influence arising from the observations that Child's C cases existed only in group I and that PEI was performed more often in the control group. Takezaki et al. [8] studied the concurrent use of 5-FU or UFT with LTN in patients with HCC treated by TAE or AI, and their results concurred with ours. We believe that it is necessary to carry out a study involving a greater number of patients to search for a more effective therapeutic method during the period of clinical follow-up after PEI, TAE, or AI.

The previous therapy has a strong influence on the response of inoperable HCC, i.e., in cases previously treated by PEI, the mean survival time was extended and the mortality was lowered. No clear difference was found in the comparison of the mean survival time and the mortality rate among the groups as a function of the Child's classification or the tumor diameter. These results suggest that a longer survival period can be expected at present if the HCC can be discovered when PEI is applicable.

The reason for starting the present cooperative study was the hope of discovering a better therapeutic method for use during the period of maintenance after PEI, TAE, or AI therapy. The authors think that further study is needed in the future regarding the kinds of BRMs, their dosage, administration frequency, and other factors so as to achieve better maintenance therapy for HCC after induction of remission.

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